Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Numerous new therapies are under investigation, but the most promising – and closest to market – are Alcon's anecortave and Bausch & Lomb's Envision TD. Anecortave looks as if it could give QLT's Visudyne a run-for-its money in AMD treatment, though there are still questions about efficacy and side effects. There was little new information at this meeting on Envision, a back-of-the eye therapy for diabetic macular edema and posterior uveitis. The prostaglandin marketing wars continue, and the hyperemia issue with Allergan's Lumigan is causing doctors to look harder at Alcon's Travatan, with use of both Lumigan and Travatan increasing at the expense of Pharmacia's Xalatan. No pickup is in sight this year for refractive surgery.

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Following is a look at some select topics, drugs, and devices from this meeting.

AGE-RELATED MACULAR DEGENERATION

The incidence of AMD is increasing, but it is unlikely that one treatment will help all patients because AMD really is a group of conditions that share some feature and symptomatic problems but actually are a group of different disorders. Visudyne has become the standard of care for predominantly classic wet AMD, but there are a number of novel medical approaches under investigation for AMD (and, often, for other eye diseases and disorders as well). A speaker said, "It seems implausible that one treatment will work for all types of AMD, so we need to match therapy to pathophysiology. If a treatment is okay but not great, then you don't want to give that to a person at a late stage."

A speaker had some warnings about anti-angiogenesis agents:

- Intraocular injections doesn't mean there is no systemic spillover.
- Systemically administered anti-angiogenesis agents will be risky in ARRMS. These patients often have cerebral and myocardia ischemia, but local delivery is worth investigating.
- Inhibition of angiogenesis in ischemic retinopathies may have significant consequences. It is possible the retina will massively infarct.

ALCON'S Anecortave Acetate (AL-3789) is delivered around the back of the eye, where it diffuses across the choroid into the macular portion of the retina. The delivery method is a juxtascleral injection. First a drop of local anesthesia is administered, then a small (1mm-2mm) incision is made from the limbus through the Tenon's space using a specially-designed, single-use cannula. No sutures are required. The drug comes in a vial, not a pre-filled syringe.

Researchers are fairly optimistic about the outlook for anecortave. Among their comments:"

- "We participated in the trial, and the results are very encouraging."
- "There was no increased risk of glaucoma or cataracts with this treatment."
- "Patients on anecortave don't leak! The results have been great. After just Visudyne, 90% of patients leaked. Combining Visudyne and anecortave reduces the number of patients who need re-treatment with Visudyne."
- "I think it looks good. The company makes us re-treat patients when they don't need it, but it does dry up leaks, and it is safe."

Alcon researchers presented data at ARVO on three Phase II studies (C-00-41, C-00-07, and C-98-03) of anecortave for the treatment of wet AMD. A speaker said there were no important safety issues raised by any of these trials, "One hundred ninety-five patients have been treated up to five times, with a total exposure up to 30 months, and there have been no clinically relevant side effects. There was some ptosis, subconjunctival hemorrhage, ocular pruritis, etc., but only one side effect was higher in the drug arm -- ocular pain. We've seen a lot of that in our office, but it was transient and mild, resolving within 72 hours and did not interrupt treatment." Another researcher said, "There is some transient ocular pain and redness." A third commented, "The infection rate is almost zero. Patients will tolerate this."

Anecortave Side Effects

Trial and side effects	Anecortave	Placebo
Ocular pain		
C-98-03 monotherapy	18%	10%
C-00-07 combination therapy	19%	9%
Ocular hyperemia		
C-98-03 monotherapy	8%	3%
C-00-07 combination therapy	19%	24%
Ptosis		
C-98-03 monotherapy	17%	20%
C-00-07 combination therapy	4%	2%
Ocular pruritis		
C-98-03 monotherapy	13%	27%
C-00-07 combination therapy	3%	2%
Subconjunctival hemorrhage		
C-98-03 monotherapy	13%	13%
C-00-07 combination therapy	1%	7%

C00-07. This six month, double-masked, randomized study of anecortave as a single injection following photodynamic therapy (PDT) with Visudyne is complete.

- There were 136 patients at 11 sites, with three arms:
  - 45 patients at 30 mg anecortave plus PDT
  - 45 patients at 15 mg anecortave plus PDT
  - 46 patients with PDT alone
- 60% of patients had predominantly classic AMD and 40% had "mostly classic" AMD.
- The study found no statistically significant difference between anecortave and placebo in terms of maintaining visual acuity (measured as the loss of less than three lines of vision), though there was a trend suggesting that anecortave treatment following PDT maintains visual acuity better than PDT alone.

Results of C-00-07 Anecortave/PDT Trial

Endpoint	Anecortave plus PDT	PDT alone
<3 lines vision loss	78%	67%
No PDT re-treatment required during the trial	22% (30 patients)	16%

- There were 128 patients (79% with predominantly classic AMD and 21% with "mostly classic" AMD) at 18 sites in this study.
- There are four arms: 30 mg (n=33); 15 mg (n=33), 3 mg (n=32) and placebo (n=30).
- The study objective was the retrobulbar depot effect on visual acuity changes and CNV lesion growth.
- The study is ongoing with 54 active patients, and 12 month data on all patients: 78 have had a second injection so far, 57 got three injections, 31 patients have had four injections, and 11 got five injections.
- A six-month intent-to-treat analysis of this ongoing 24-month trial found that patients treated with 15 mg anecortave demonstrated significantly less change in lesion growth, including choroidal neovascularization, than patients treated with placebo.

Results of C-98-03
Anecortave Acetate (AA) Monotherapy Trial

Endpoint	30 mg AA	15 mg AA	3 mg AA	Placebo
<3 lines vision loss	75%	88%	75%	70%
≥2 lines vision improvement	18%	N/A	6%	0%

C-00-41. This is an ongoing, 12-month, open-label study of 30 mg Anecortave injections at six-month intervals. PDT with QLT's Visudyne (verteporfrin) was allowed if the patient met the label criteria for that agent. There were 34 patients enrolled, and they got up to two injections of anecortave.

Several questions were raised about the anecortave trials:

- There was a lack of dose-response curve. Only the middle, 15 mg, dose showed a statistically significant response over placebo, not the lower or higher dose. Asked why the higher 30 mg dose didn't show a better effect than the 15 mg, a researcher said, "We reached a peak dose effect at 15 mg." Another expert said, "Watch this lack of dose response, because it doesn't make sense."
- The drop out rate appears fairly high. Company officials did not have a good explanation for this and could not identify the arms the drop-outs were in. One researcher said, "Some left because of logistics, and some because their vision worsened."
- The number of patients in the trial, and in each arm, was small.

- There was an "abnormal vision" side effect reported in all the trials. This appeared to be a catch-all category described as "mild, transient changes typical of the disease being treated," and included such things as increased metamorphopsia, flashes, black spots, dancing lights, etc. In all cases it reportedly occurred in the fellow eye as well as the treated eye. In the monotherapy trial (C-98-03) and the PDT combination trial, this did not occur at the 15 mg dose. A company official, asked about this, at first dismissed it as a feature of the disease, though, of course, the placebo patients also had the disease. A researcher pointed out, "The abnormal vision didn't occur in the 15 mg dose trial, only in the 3 mg and 30 mg doses."

Abnormal Vision Side Effect

Trial	All Anecortave Patients	Placebo
Combination with PDT (C-00-07)	4% at 30 mg only	2%
Monotherapy (C-98-03)	13% at 3 mg and 30 mg only	0%
Open label study (C-00-41)	6% (dose N/A)	N/A

A two-year, pivotal Phase III trial comparing 15 mg anecortave head-to-head with Visudyne was being designed and was expected to start soon. A doctor who participated in a Phase II anecortave trial had reservations about participating in this trial, "I'd rather use combination therapy – anecortave the same day or within a few days of Visudyne. Visudyne is now the gold standard in AMD, and I can't see breaking that."

Two issues may affect this trial:

1. Recruitment. An investigator working on the Phase III trial admitted it may be hard to recruit patients for this study, but he said the company would go forward with it anyway.
2. QLT is running the VER trial looking at re-treating patients with Visudyne every six weeks instead of every 12 weeks. If that trial is positive, it could make a trial design correction necessary in the anecortave Phase III trial, a researcher said.

EYETECH's anti-VEGF Aptamer, EYE001, is an oligonucleotide that acts like an antibody and binds VEGF. It reportedly utilizes a new transcleral delivery system with microspheres that releases 2 µg/day over 20 days. Researchers who have worked with this agent were fairly optimistic about it. One said, "There were no randomized controls, no long-term follow-up, no large sample size – so no conclusions. But this is green light for a Phase III pivotal trial." EyeTech also has begun a DME study of Aptamer.

The two AMD Aptamer trials discussed at this meeting were:

- A 15-patient Phase Ia trial of a single injection.
- An 8-patient Phase IIa trial comparing monthly Aptamer injections alone to monthly Aptamer injections plus every three month PDT.

Aptamer (EYE001) Phase I and II Results

Therapy	Vision stabililized or improved	3-line or better improvement in vision
Aptamer Phase Ia (n=15)	80.0%	26.7%
Aptamer Phase IIa (n=8)	87.5%	25.0%
Combined Aptamer trials (n=23)	82.6%	26.1%
PDT reported results	50.5%	2.2%
PDT controls	44.0%	1.4%
Radiation controls	48.0%	3.0%

Among the issues being watched with this agent:

- Method of action. It acts as a binding protein, but a researcher said, "No one knows why it binds."
- Length of action. It isn't known yet how long the effect lasts.
- Possible systemic effects. A source said, "Aptamer has been found in serum this is a small molecules, and it can go anywhere."

GENENTECH's VEGF-F(ab) fragment antibody is a once-a-month intravenous agent. A low dose was tested in a Phase Ib trial, and a higher dose in another Phase Ib trial. The company is expected to make a go/no-go decision before the end of the year, and if it goes ahead with testing is expected to go directly to a Phase III, skipping any Phase II trials.

GENVEC uses an intravitreal injection (straight injection into the vitreal cavity) to deliver PEDF, an anti-angiogenic agent, via an adenovirus vector. The company reportedly is preparing an IND, and a 12-month, Phase I, dose-escalating trial (starting at $1x10^6$ and increasing in half-log increment) was due to start this summer in AMD. A researcher said, "Genentech's VEGF has a short half-life and you have to give a high dose to get an effect. GenVec gets the cell to spit out PEDF – the therapeutic protein – for two or three months."

The company reportedly also is looking at other applications for this agent. A researcher said, "Theoretically, it should work in DME and posterior uveitis. The company is considering a trial to start in late 2002 or early 2003 in DME and one I proliferative diabetic retinopathy."

ISIS and **MEDIMMUNE** are working on avB3 and an anti-alpha-vBeta 5 (avB5) selective antibodies, which reportedly have shown good efficacy and no toxicity.

MERCK KGA is working on avB3 and avBR selective small molecules.

NOVARTIS has a somatostatin analog, an injectible (qM) form of octreotide in development. This was in a 300-patient Phase II trial that reportedly finished enrollment in spring 2002.

Among the other approaches being explored to treat AMD are:

Transpupillary Thermal Therapy (TTT). Enthusiasm for this treatment has faded somewhat, and reports are now more mixed, as doctors wait for a large trial to be completed. A Tennessee ophthalmologist said, "TTT is comparable to PDT in occult patients, but we are doing less TTT now than we were." Another doctor said, "TTT has a higher rate of early vision loss than PDT but at 24 months it is fairly comparable to PDT." A third source said, "TTT seems to be inefficient, short-lasting and sometimes dangerous." A Wisconsin doctor said, "I do half PDT and half TTT." Two doctors said they initially were doing a lot of TTT, then they cut back, but now usage is rebounding.

BRISTOL-MYERS SQUIBB's Kenalog (triamcinolone). Some ophthalmologists are using a single intravitreal injection of generic triamcinolone to limit the growth of CNV, at least in the short term. This approach also may reduce serous exudation. A Louisiana doctor said, "Over the last two years, we've done about 5,000 Kenalog injections at our clinic. We found that we have to repeat the injections every four to six months, but the drug is cheap, incredibly safe, and works very well. Another doctor said, "What's driving Kenalog use is the $800 Medicare reimbursement for intravitreal injections."

However, researchers reported at the meeting on a study which found no clinical or angiographic benefits to triamcinolone at 12 months. A speaker who participated in that study said, "We no longer treat patients with CNV in AMD with this because we can't. We don't have the results to support the treatment. We are still analyzing the data, and there is some suggestion that triamcinolone may be beneficial in occult AMD, but we are not sure yet. It also may work in diabetic macular edema (DME), but there haven't been any randomized clinical trials to prove that, and there are issues not just of efficacy but also safety. I think the treatment may have an effect, but we need trials to see how good it is and what the indications are."

Asked if giving the triamcinolone treatments more often would boost the efficacy in AMD, a speaker said, "You can retreat at six months, and I would encourage anyone looking at this to consider a six-month retreatment, if appropriate." As to safety, he said, "There was a 30% rate of intraocular glaucoma medication being required but we never had to filter a patient. One to two years after treatment, 20% developed cataracts. The concern is a so-called diffuse vitreous haze which occurs right after the injection. I've seen two of those out of 1,000 eyes. I did *not* treat these with antibiotics, and they recovered, but a colleague did and he also got good results."

PIF-6, an anti-alpha-vBeta 5 (avB5)

LM609, a monoclonal antibody which is an antagonist to the angiogenic integrin alpha v beta 3 (avB3).

Molecular genetics, which would deliver treatments long before people become symptomatic. Several studies have concluded that a significant percentage of AMD cases have a genetic component, and a speaker said, "I think AMD will prove to involve 30-40 different genes."

Surgical approaches such as:

- Surgical intervention. With removal of abnormal tissue, there is an immediate decline in acuity but then fairly stable vision for three to four years, so this is a possible way of achieving vision stability.
- Tissue relocation. In one study, 31 of 102 eyes could be evaluated at six months, and 49% showed improvement, 32% were the same, and 19% were worse. Complications were frequent, and recurrences reportedly almost always come back under new fovea, causing a researcher to conclude that this approach may be best for non-AMRD eyes.
- 360 degree approach. This is more invasive than other therapies, but it may provide good vision stability. In a study of 45 eyes, 13% improved, 53% were the same, and 33% got worse.
- Transplantation. This is not yet ready for clinical use, but it is being explored.

INTRAOCULAR DRUG DELIVERY FOR DME, POSTERIOR UVEITIS, AND GLAUCOMA

An estimated 40% of ophthalmic diseases, including glaucoma, AMD, diabetic macular edema, posterior uveitis and diabetic retinopathy, affect the posterior part of the eye, The problem in treating these diseases is that the blood-retinal barrier, like the blood-brain barrier, keeps many therapeutic agents out. Therefore, several companies are investigating intraocular drug delivery systems. Currently, the only one on the market is Bausch & Lomb's Vitrasert, a surgical implant that delivers Hoffman-La Roche's ganciclovir in a controlled-release manner, and it is used to treat CMV retinitis caused by AIDS.

Diabetic macular edema, for instance, affects up to 10% of all diabetics, or about 500,000 Americans, with 75,000 new cases occurring annually. DME is closely associated with diabetic retinopathy and the duration and type of diabetes patients have.

Incidence of DME

Type of Diabetes	Incidence at 10 years	Incidence at 20 years
Type 1 diabetics on insulin	7% - 10%	25% - 30%
Type 2 diabetics on insulin	10%	30%-35%
Type 2 diabetics not on insulin	5%	15%

Among the intraocular drug delivery devices in development are:

AP PHARMA is studying the medium-to-long-term ophthalmic biocompatibility of ophthalmic drug delivery using its Poly-Ortho Ester polymer, which reportedly is stable at room temperature and has a neutral interior pH.

BAUSCH & LOMB's Envision TD, which is a joint effort of B&L and Control Delivery Systems, has been granted fast-track status by the FDA. This technology uses a tiny drug reservoir implanted into the back of the eye that delivers a sustained and consistent level of fluocinolone acetonide directly to the affected area of the eye for up to three years. It is a polymer-based, intravitreal drug-delivery system, which is surgically placed in the back of the eye.

Initially, Envision is being investigated as a treatment for posterior uveitis and diabetic macular edema (DME). However, sources expect that B&L also will test it in AMD in the future. The final results from a pivotal, six-month, 180-patient Phase IIb/III trial in DME will be presented at the Retina Society meeting in San Francisco on September 30, 2002. In an earlier DME trial, 80 patients were randomized to standard of care (macular grid laser or observation) or a 0.5 mg implant. The primary endpoint in this trial was a change in macular edema at six months compared to baseline (as assessed by retinal thickening). Compared to standard of care, patients with Envision showed:

- a statistically significant improvement in macular edema
- a greater improvement in the severity of their diabetic retinopathy
- >80% improved or stable visual acuity (vs. 50% with standard of care)
- comparable adverse events (18% with Envision, 15% with standard of care). These included cataracts, vitreous hemorrhage, retinal neovascularization and ocular hypertension – all expected side effects with this disease and drug. No patients required implant removal or withdrew from the study due to an adverse event.

A Phase III trial in posterior uveitis is underway comparing: a) implant alone, b) implant with vitrectomy, and 3) placebo implant.

The areas of concern with Envision in DME that doctors are watching include:

- **Design modifications.** The device has had to be re-designed at least twice, and some doctors predicted that further modifications will be required before approval. A researcher reported that one batch released in eight months, much quicker than the expected three years, but he said this has not delayed any of the trials, "We started the DME trial with the new design in January 2002." Another researcher said, "The device is not ready for prime time. I expect it to undergo several more changes before it is ready for FDA approval. The device was changed because the drug release was erratic, and the problem was worst at low doses."
- **Dosage.** In the pivotal trial, B&L is using the 0.5 mg dose, but the 2 mg dose tried in the first DME trial was dropped because it did not show any additional benefits over 0.5 mg. A researcher said the company now is testing a 0.1 mg dose, "The dose (0.15 mg) is still too high; 0.1 is not as effective, but the risk of cataracts and glaucoma is lower."
- **Trial size.** The pivotal trial is a 180-patient study. Some sources have suggested that the FDA may want 300 eyes, but most researchers thought the trial would be large enough to satisfy regulators.
- **Trial length.** The device delivers a steroid over three years, but the DME trial is only six months long, and the posterior uveitis trial is only 12 months long.
- **Hypotension.** This is the most concerning side effect, though in the study, so far, it reportedly has been adequately treated with eye drops when it occurs.

CEPHALON's CEP-7055 is an oral agent and, in animals, reportedly showed sufficient retinal bioactivity to suppress both VEGF and diabetes-induced retinal vascular permeability, suggesting that this and related compounds may have value in diabetic macular edema and related disorders.

Eli LILLY has LY333531, an oral PKC-β inhibitor, in Phase III development for diabetic macular edema.

NEUROTECH S.A., a French based biotechnology company, is developing controlled-release therapies, using its proprietary Encapsulated Cell Technology to delivery protein drugs in the eye and the central nervous system.

NOVARTIS has an oral PKC antagonist for diabetic macular edema. The results from a Phase II trial should be available soon, a source reported.

OCULEX has a partnership with Allergan and is recruiting patients for its steroid-delivering, back-of-the-eye device. This device that works similarly to Envision, but is smaller than Envision, is biodegradable, and uses a different steroid. It is being tested in central vein occlusions, branch vein occlusions and AMD.

GLAUCOMA

Most of the pharmaceutical attention in glaucoma arena was on the prostaglandin wars, with Pharmacia (Xalatan, latanoprost), Alcon (Travatan, travopost), and Allergan (Lumigan, bimatoprost) all were trying to convince doctors their product was best of these treatments.

A speaker tried to differentiate Lumigan from the prostaglandins – Travatan and Xalatan – and claimed that it is more effective. He said, "Lumigan is more effective than Xalatan, it can be additive to Xalatan, and it works in patients non-responsive to Xalatan." The points he made in support of this were:

- Animal studies of Lumigan, at seven time the clinical dose, found only low levels of the acid metabolite in the ciliary body – too low to be pharmacologically relevant.
- Lumigan acts directly – not as a prodrug.
- Acts on the prostamide receptor. "We have functional evidence for the existence (e.g., in cat eye) of prostamide receptors, but we have not cloned the receptor gene."
- Prostamides act on different, unique receptors.
- Lumigan does not act through prostaglandin receptors.
- Lumigan has inherent pharmacological activity.

Another speaker reviewed Lumigan data, claiming that Lumigan is better at controlling intraocular pressure (IOP) than timolol, Xalatan, and Merck's Cosopt (dorzolamide). He also argued that Lumigan plus Allergan's Alphagan (brimonidine 0.2%) is better than Xalcom (Xalatan plus timolol).

However, doctors are not convinced, and the sleeper – or come-from-behind kid -- in this category appears to be Travatan. A glaucoma expert said, "The hassle factor is important. Drugs that cause side effects cause too much hassle for doctors as well as patients. Lumigan causes red eye (hyperemia) in too many patients – and it doesn't go away in most patients. Allergan even has a patient handout that tells patients not to call their doctor if their eye gets red."

ALLERGAN:

- AlphaganP (brimonidine 0.15%), the new version of Alphagan with Purite (sodium chlorite) as the preservative, also got a big push at the meeting. A speaker pointed out that its preservative is Purite instead of BAK and the concentration of drug is lower than with Alphagan, yet with the same efficacy and safety as Alphagan. AlphaganP also reportedly causes less allergic conjunctivitis, less oral dryness, less conjunctival hyperemia, less eye discharge and less somnolence than Alphagan.

- Combigan is a combination of Alphagan and timolol, but sources were not optimistic about any quick FDA approval for this. One doctor said, "The FDA is hesitant to approve combinations. Pharmacia had to do another trial of its Xalcom (Xalatan+timolol). The FDA keeps sending Xalcom back for more studies. Allergan also is likely to have trouble getting Combigan approved." An Allergan official said the company cannot or will not develop a CombiganP (combination of AlphaganP+ timolol).

PHARMACIA's Xalcom (Xalatan .005% + timolol .5%) got little attention at the meeting. It has been approved in Europe, but the FDA wanted more data.

Three-Month Phase IIIb Data

Drug	8 am average IOP	12 noon average IOP	4 pm average IOP	Adverse Events
Xalatan	9.59	9.09	9.64	28.8%
CoSopt	8.37	8.82	8.23	34.4%
p-value	.007	nss	.001	---

TEVA PHARMACEUTICALS is investigating Copaxone (copolmer-1) – which is approved to treat multiple sclerosis – as a treatment for glaucoma. The drug reportedly is being reformulated, perhaps into a topical agent.

NEUROPROTECTION

Neuroprotective drugs – like Forest Laboratories' memantine – have shown efficacy in animals but so far human trials in stroke have failed. Yet, ophthalmologists are still hopeful they will prove useful in eye disorders like glaucoma. A speaker suggested the reason neuroprotectives may work in glaucoma is that glaucoma is an axogenic (white matter) disease, not a somagenic (gray matter) disease, "In axogenic disease, the ganglocyte takes days or weeks to die, so the window of opportunity for therapy is longer. The reasons glaucoma is likely a good target is that neuroprotection can be achieved in animal models of glaucoma. Personally, I think these will work."

REFRACTIVE SURGERY

Doctors at this meeting were not optimistic about the outlook for the refractive surgery market for the rest of this year. Sources said:

- No pickup before late 2002 was expected.
- The laser machine market was considered saturated.
- Refractive procedures year-to-year were flat.
- Custom ablation was generating little excitement. A Pennsylvania doctor said, "There is not a dramatic difference in outcomes using custom ablation."

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